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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,787	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☒ Claim(s) *123(as it reads on species nn), 158 and 166* is/are allowed.

6)☒ Claim(s) *84,119,121,164,165 and 210-214* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 39-45,47-51,53,56-66,68,69,74-78,80,82,84-89,91,92,94-104,106,107,112-116,118-121,123-128,130,133-143,145,146,151-155,157-159 and 164-214.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 47-51,53,54,56-66,68,69,74-78,80-82,85-89,91,92,94-104,106,107,112-116,118,120,124-128,130,133-143,145,146,151-155,157,159 and 167-209.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 14, 2005 has been entered.

2. Claims 39-45, 47-51, 53, 56-66, 68-69, 74-78, 80, 82, 84-89, 91, 92, 94-104, 106, 107, 112-116, 118-121, 123-128, 130, 133-143, 145, 146, 151-155, 157-159 and 164-214 are pending.

Claims 38, 81 and 163 have been canceled.

Claims 84, 121 and 166 have been amended.

Claims 47-51, 53, 56-66, 68, 69, 74-78, 80, 82, 85-89, 91, 94-104, 106, 107, 112-116, 118, 120, 124-128, 130, 133-143, 145, 146, 151-155, 157, 159 and 167-209, drawn to non-elected inventions are withdrawn from examination.

Claims 84, 119, 121, 123, 158, 164-166 and 210-214, which read on the elected species, nn. is examined on the merits.

Withdrawn Objections

Specification

3. The disclosure is no longer objected to because the embedded hyperlink and/or other form of browser-executable code on page 33, lines 5, 6 and 10 has been deleted according to the amendment to the specification submitted October 15, 2004 and noted in the Remarks, see page 20.

Claim Objections

4. Claims 38 and 163 are no longer objected to because they have been cancelled.

Sequence Compliance

5. Applicants assert that the sequences of record within several pages and several tables of the specification are compliant with the requirements of 37 C.F.R. §§ 1.821-1.825, see Remarks submitted October 15, 2004, pages 21 and 22.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

6. The rejection of claims 123, 158 and 166 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn. Claims 38, 81 and 163 have been cancelled.

7. The rejection of claims 123, 158 and 166 under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. Claims 38, 81 and 163 have been cancelled.

Claim Rejections - 35 USC § 102

8. The rejection of claims 123, 158 and 166 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent application publication number US2002/0052308A1 (May 2, 2002) is withdrawn. Claims 38, 81 and 163 have been cancelled.

Claim Rejections - 35 USC § 103

9. The rejection of claims 84, 119, 121, 122, 158 and 164-166 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent application publication number US2002/0052308A1 (May 2, 2002) is withdrawn. Claims 38, 81 and 163 have been cancelled.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The rejection of claims 84, 119, 121, 164 and 165 and newly added claims 210-214 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained and made. Claims 38, 81 and 163 have been cancelled.

Applicants aver in the Remarks submitted October 15, 2004 on pages 23 and 24 that particular claims have been cancelled to expedite prosecution and have amended independent claim 84 to include the fusion protein has the defined C35 peptide as well as a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin, and a marker sequence. Applicants note they do not need to provide sequence of these heterologous proteins because they are known. These points of view have been carefully considered, but found unpersuasive.

Claims 84, 119, 121, 164, 165 and 210-214 broadly claim a fusion protein comprising at least one C35 peptide epitope defined as I-105 to V-113 of SEQ ID NO: 2 and a polypeptide selected from the group consisting of a heterologous epitope, a

heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin, and a marker sequence. The written description in this instant case only sets forth polypeptide, SEQ ID NO: 2 consisting of 115 amino acid residues and including the defined epitope consisting of I-105 to V-113. The written description is not commensurate in scope with the claims drawn to a fusion protein comprising the defined sequence of I-105 to V-113 and arbitrary polypeptides such as a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunoglobulin, and a marker sequence. These additional amino acids are not adequately described therefore one of ordinary skill in the art does not have explicit information regarding for example, the amino acid residues, the size of the polypeptides, the structure of the polypeptides. Consequently, the fusion protein comprising the defined C35 peptide epitope and undefined amino acid sequences is not exemplary of Applicants' possession of the claimed fusion polypeptide.

Applicants attest that heterologous proteins are known and cite case law in support of this assertion, see Remarks, bridging paragraph of pages 23 and 24. The broadly claimed genus of fusion proteins in its entirety is not reasonably in possession of Applicants. While Applicants clearly are in possession of SEQ ID NO: 2 including the amino acid sequence, I-105 to V-113 the balance of the fusion protein is unknown and there is no nexus presented between the structure and the function of the fusion protein. "[W]hen there substantial variation within the genus, one must describe a sufficient

variety of species to reflect the variation within the genus", see Official Gazette, 1242 OG 174, first column, January 31, 2001.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO: 2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

At the time the application was filed Applicants only had possession of SEQ ID NO: 2 containing the amino acid epitope, I-105 to V-113 and not fusion polypeptides that include undefined amino acid sequences. The fusion protein potentially contains at least 107 amino acids that have not been described. Likewise the fusion protein that comprises one C35 peptide epitope is surrounded by amino acids not described in the specification. The broad claim reads on a plethora of polypeptides of any length, hence there is no sufficient evidence presented in the Remarks or of record of Applicants' possession of such a huge group of polypeptides. And while Applicants do not have to list every species within a claimed genus, there must be a representative number of species presented. The specification does not evidence the possession of all the possible fusion proteins the claims encompass.

Applicants state and point out in the specification description of the use of epitopes in cancer treatment, cancer diagnosis, prognostic testing and treatment, see Remarks page 25. While this prophetic teaching is listed in the specification it does not support Applicants having written description for the claimed genus of molecules encompassed by the claims. There is insufficient to support the generic claims as

provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Based on the analysis set forth above and of record the full breadth of the claims do not meet the written description provision of 35 U.S.C. 112, first paragraph.

12. The rejection of claims 84, 119, 121, 164, 165 and newly added claims 210-214 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention is maintained and made. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claims 38, 81 and 163 have been cancelled.

"Applicants assert that adequate guidance and direction is provided with respect to the claimed invention.", see Remarks, page 26. Applicants further asset the specification provides that C35 polypeptides and fusion proteins that comprise CTL epitopes are useful in the treatment of C35-specific cancers and express where in the disclosure support can be found for a C35 epitope killing breast cancer cells. Applicants aver that the specification provides adequate guidance and fusion proteins do not need to have the same function as wild type C35 polypeptides. These arguments have been condisdered, but found unpersuasive.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQZd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a fusion protein comprising at least one C35 peptide epitope, I-105 to V-113 and a polypeptide sequence selected from the group consisting of a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunogloubulin and a marker sequence comprised within a pharmaceutically acceptable carrier. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to a fusion protein comprising a defined C35 peptide sequence, I-105 to V-133 (a peptide within full length sequence, SEQ ID NO: 2) and undefined amino acid sequences broadly identified as a heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunogloubulin and a marker sequence. The breadth of the claims is vast and not reasonably supported by the specification.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunogloubulin and a marker sequence have not been clearly defined by the specification. Moreover, it is not clear what the limits are of a "part of a constant domain". This recitation in itself reads on a couple of amino acids or many amino acids. While it is clear Applicants desire to implement these fusion proteins in the treatment of C35-specific cancers, in diagnostic and prognostic applications it would require significant study to identify, make and use the exponential amount of fusion proteins that are applicable to treatment, diagnosis and prognosis.

The unpredictability of the art and the state of the prior art

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different

biological activity from the wild type protein. And even though Applicants assert the fusion proteins comprising C35 peptides do not need to have the same function as a wild type C35 polypeptides it would seem the amino acid sequences surrounding the C35 peptides (i.e., amino terminal, carboxy terminal) would affect structure and function of the fusion proteins and inevitably influence their use in the suggested applications.

Working examples/ Guidance in the specification

Applicants submit in Example 2 on pages 227-229 of their specification show that CTLs specific for a C35 epitope kills breast cancer cells and the specification provides adequate guidance as to how C35 epitopes can be used, see Remarks, page 26. This teaching does not provide for the full scope of the fusion proteins with a C35 peptide with the undefined amino acid sequences listed as heterologous epitope, a heterologous signal sequence, a heterologous functional domain, part of the constant domain of an immunogloubulin and a marker sequence. Moreover, the specification provides insufficient guidance in terms of the selection of these sequences. This would force one of skill in the art to determine through trial and error which fusion proteins would be effective for treatment, diagnosis and prognosis. The disclosure provides insignificant objective evidence and insufficient working examples to lead one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable art such as treatment, diagnosis and prognosis with a fusion protein comprising 9 amino acids and an undefined upper limit of additional amino acids. In the instant case, the claims are so

broadly drawn, the guidance so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make and use the fusion proteins as broadly written.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed amino acids in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which must be made in the amino acid sequence of SEQ ID NO: 2, which results in limited sequence identity and/or undefined substitutions and consequent use of these variants in the applications outlined in specification is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 84, 119, 121, 164 and newly added claims 210-214 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 84 is vague and indefinite in the recitation "a heterologous functional domain". It is not clear what functions the domain should possess. Accordingly, the metes and the bounds cannot be determined.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. The rejection of claims 84, 119, 121, 164, 165 and newly added claims 210-214 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent application publication number US2002/0052308A1 (May 2, 2002) is maintained and made. Claims 38, 81 and 163 have been cancelled.

Applicants assert that publication US2002/0052308A1 discloses SEQ ID NO: 9666, a protein 131 amino acids in length and reads on Applicants' claimed fusion protein, however the publication does not teach or suggest the fusion protein of claims

84, 119, 164 or 165. These observations and arguments have been fully considered but found unpersuasive.

Applicants were provided with a sequence alignment between Applicants' SEQ ID NO: 2 and the publication's SEQ ID NO: 966 with the action mailed August 27, 2003 as Paper number 22. Sequence number 966 of U.S. Patent application publication # US2002/0052308A1 discloses an isolated polypeptide comprising a peptide epitope, I-121 to V-129 which is the same as Applicants' C35 peptide epitope, I-105 to V-113 of SEQ ID NO: 2. The disclosed C35 peptide epitope is comprised amongst 122 additional amino acids, which reads on Applicants' claimed fusion protein. "[A]ny polypeptide of the present invention can be used to generate fusion proteins.", see page 191, section 0118. Moreover, "the polypeptides of the present invention, and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention maybe fused with the constant domain of immunoglobulins...or portions thereof...", see page 190, section 0112. "The polypeptides of the present invention can be fused to marker sequences", see page 191, section 0114. Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions.", see page 191, section 0119. Also disclosed is a pharmaceutical composition comprising the disclosed peptide epitope, see page 208, sections 0258-0260.

Allowable Subject Matter

17. Claims 123 (as it reads on species, nn. amino acids I-105 to V-113 of SEQ ID NO :2), 158 and 166 are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 5:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
31 March 2005